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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/537,758

06/06/2005

Mark E. Fraley

20977P

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7590

10/10/2006

MERCK AND CO., INC  
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RAHWAY, NJ 07065-0907

EXAMINER

BALASUBRAMANIAN, VENKATARAMAN

ART UNIT

PAPER NUMBER

1624

DATE MAILED: 10/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/537,758

Applicant(s)

FRALEY ET AL.

Examiner

Venkataraman Balasubramanian

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 06 June 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-13,15-19,21,32 and 33 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-13,15-19,21,32 and 33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 10/19/05, 12/23/05.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

The preliminary amendment, which included cancellation of claims 14, 20, 22-31 and 34-38, filed on 6/6/2005, is made of record. Claims 1-13, 15-19, 21, 32 and 33 are now pending.

#### ***Information Disclosure Statement***

References cited in the Information Disclosure Statements, filed on 10/19/2005 & 12/23/2005, are made of record.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-19, 21, 32 and 33 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating breast cancer, does not reasonably provide enablement for preventing or treating any or all cancer, treating or preventing any or all diseases wherein angiogenesis is implicated, treating or preventing retinal vascularization, treating or preventing diabetic retinopathy, treating or preventing age-related macular degeneration and treating or preventing retinal ischemia. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant claims method of use claims 13, 15-19, 21, 32 and 33 are drawn to preventing or treating any or all cancer, treating or preventing any or all diseases wherein angiogenesis is implicated, treating or preventing retinal vascularization,

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treating or preventing diabetic retinopathy, treating or preventing age-related macular degeneration and treating or preventing retinal ischemia.

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of kinase by the instant compounds, instant claims reaches through inhibiting and treating any or all diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of kinase, based on limited assay, it is claimed that treating or preventing any or all cancer, treating or preventing retinal vascularization, treating or preventing diabetic retinopathy, treating or preventing age-related macular degeneration, treating or preventing retinal ischemia etc in general. The scope of the claims includes any or all cancer, any or all diseases wherein tyrosine kinase is implicated by tyrosine kinase inhibition including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 50-58. The instant compounds are disclosed to have tyrosine kinase receptor inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all

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diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode of action as kinase inhibitor that would be useful for all sorts of proliferative diseases and cancers, inflammatory diseases and others which involve tyrosine kinase pathway. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as psoriasis and cancers , vascular diseases are very difficult to treat and despite the fact that there are many drugs, which can be used for "inhibiting tyrosine kinases".

In addition, the scope of the instant claims include preventing any or all diseases wherein tyrosine kinase is implicated, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate or counter in advance, to keep from happening etc.* (as per Webster's II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

The scope of the claims involve large number of compounds of claims 1-10 as well as the thousand of diseases embraced by the terms cancer, vascular and ocular diseases.

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Proliferative disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the *Helicobacter pylori* infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless. .

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001, wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the

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instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Hasan et al. Expert Opin. Biol. Ther. 1(4): 703-718, 2001 and Pegram et al. Semin. Oncol. 29(3) Suppl11) 29-37, 2002 (PubMed Abstract provided).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

- 1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require tyrosine kinase receptor inhibitory activity.
- 2) The state of the prior art: Recent publications expressed that the tyrosine kinase receptor inhibition effects are unpredictable and are still exploratory. See references cited above.
- 3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely

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with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of tyrosine kinase receptor inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all diseases and cancers including those yet to be related to tyrosine kinase.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or

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use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 11-13, 15-19, 21, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Bilodeau et al., US 6,380,203.

Bilodeau et al., teaches several pyrazolo(1,5-a)pyrimidines their composition and method of use which include compounds, composition and method of use embraced in the instant claims. See formula I and note when R<sub>1</sub> is phenyl or substituted phenyl and R<sub>4</sub> is aryl, heteroaryl or heterocyclyl, the compounds taught by Bilodeau et al. include instant compounds. See entire document especially column 6 for various species and column 7-16 for various process of making and compounds made. See examples 1-6. See claims 114, particularly claim 2 for several species which include instant compounds.

Claims 1-4, 11-13, 15-19, 21, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Bilodeau et al., WO 00/53605.

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Bilodeau et al., teaches several pyrazolo(1,5-a)pyrimidines their composition and method of use which include compounds, composition and method of use embraced in the instant claims. See page 5, formula I and note when R<sub>1</sub> is phenyl or substituted phenyl, with the given choices of R<sub>10</sub>, the compounds taught by Bilodeau et al. include instant compounds. See entire document especially pages 5-10 for preferred embodiments, pages 11-12 for various species and pages 20-23 for various process of making and compounds made. See example 2, which include instant compound.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13, 15-19, 21, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bilodeau et al., US 6,380,203.

Teachings of Bilodeau et al., as discussed in the above 102 rejection is incorporated herein. As noted above, Bilodeau et al., teaches several pyrazolo(1,5-a)pyrimidines their composition and method of use which include compounds, composition and method of use embraced in the instant claims.

Instant claims require variously substituted phenyl in the 6-position of the pyrazolo(1,5-a)pyrimidine. Bilodeau et al., as noted above teaches mainly unsubstituted phenyl. However, Bilodeau et al., teaches equivalency of those compounds exemplified with those generically claimed for compound of formula I.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in pyrazolo(1,5-a)pyrimidine ones as permitted by the reference and expect resulting compounds (instant compounds) and their composition possess the uses taught by the art in view of the equivalency teaching outline above.

Claims 1-13, 15-19, 21, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bilodeau et al., WO 00/53605.

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Teachings of Bilodeau et al., as discussed in the above 102 rejection is incorporated herein. As noted above, Bilodeau et al., teaches several pyrazolo(1,5-a)pyrimidines their composition and method of use which include compounds, composition and method of use embraced in the instant claims.

Instant claims require variously substituted phenyl in the 6-position of the pyrazolo(1,5-a)pyrimidine as well as variously substituted aryl or heterocyclyl for A. Bilodeau et al., as noted above teaches mainly unsubstituted phenyl and heterocycle substituted with alkylheterocycle as seen in example 1 and 2. However, Bilodeau et al., teaches equivalency of those compounds exemplified with those generically claimed for compound of formula I.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in pyrazolo(1,5-a)pyrimidine ones as permitted by the reference and expect resulting compounds (instant compounds) and their composition possess the uses taught by the art in view of the equivalency teaching outline above.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

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F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13, 15-19, 21 32 and 33 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,380,203. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds, composition and method of use embraced in the instant claims are embraced in the claims 1-14 of US 6,380,203 as discussed in the above 102/103 rejections.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in pyrazolo(1,5-a)pyrimidine ones as permitted by the reference and expect resulting compounds (instant compounds) and their composition possess the uses taught by the art in view of the equivalency teaching outline above.

Claims 1-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,245,759. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and their composition embraced in the instant claims are embraced in the claims 1-3 of US 6,245,759 as discussed in the above 102/103 rejections under *Bilodeau et al.*, WO 00/53605.

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Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in pyrazolo(1,5-a)pyrimidine ones as permitted by the reference and expect resulting compounds (instant compounds) and their composition possess the uses taught by the art in view of the equivalency teaching outline above.

Claims 12,13, 15-19, 21 32 and 33 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,544,988. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of use embraced in the instant claims are embraced in the claims 1-13 of US 6,544,988.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in pyrazolo(1,5-a)pyrimidine ones as permitted by the reference and expect resulting compounds (instant compounds) and their composition possess the uses taught by the art in view of the equivalency teaching outline above.

### **Conclusion**

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any

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inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

  
Venkataraman Balasubramanian

9/29/2006